



DAVINCI
MEDICAL
ACADEMY

SUBJECTS IN NUTSHELL FOR EFFECTIVE REVISION



PHYSIOLOGY IN NUTSHELL

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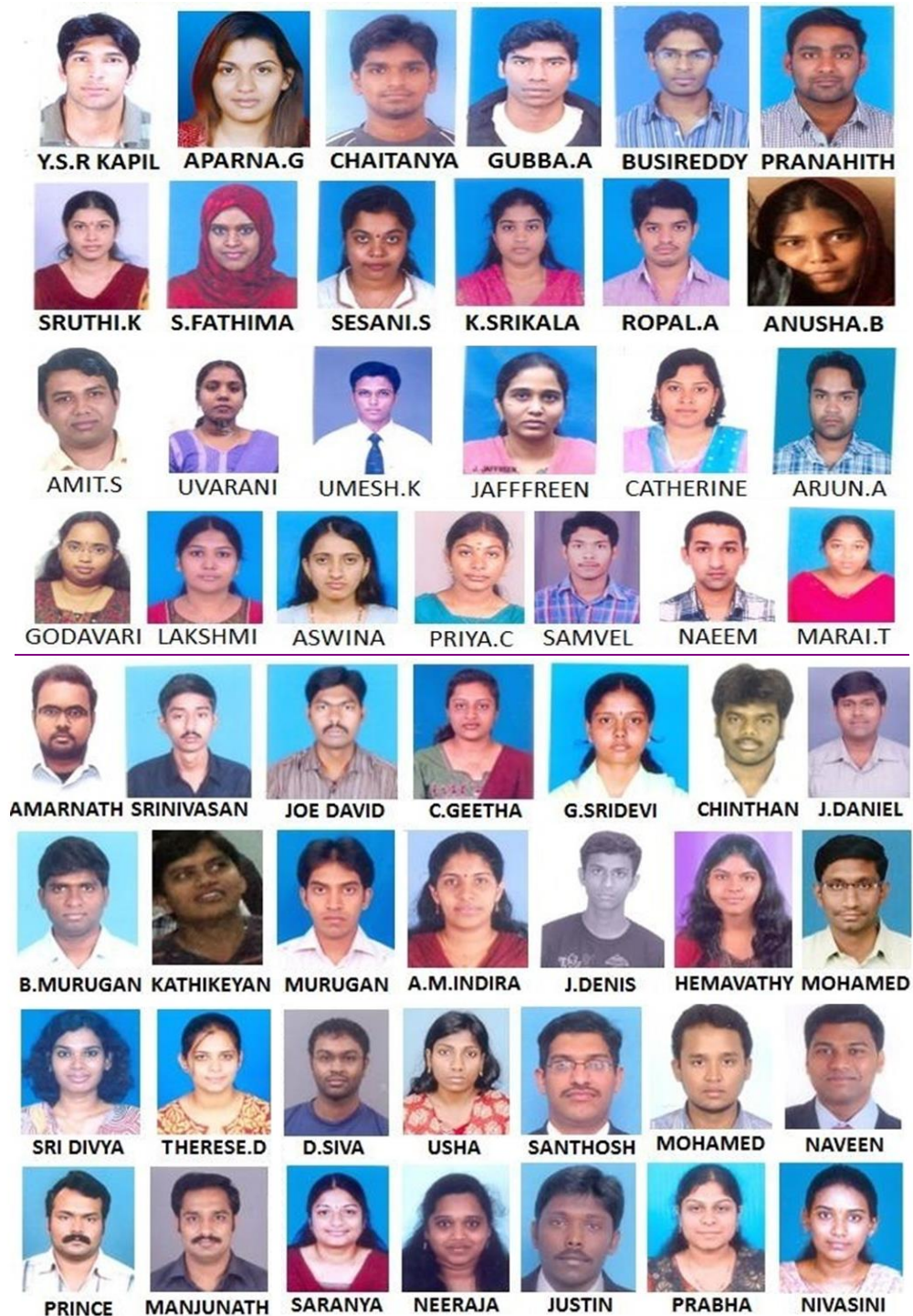
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ELITE TEAM OF FACULTY



SOME OF OUR FMGE TOPPERS



DMA'S CORNER OF WISDOM

GENERAL PHYSIOLOGY

HISTORICAL BACK UP

- Father of Physiology- **Claude Bernard**.
- The term 'homeostasis' (**milieu interior**) was coined by – **Walter.B.Cannon**.
- The scientist who first proposed that all life mechanisms are aimed at maintaining the constancy of composition of the internal environment - **Claude Bernard**.

FEEDBACK MECHANISMS

Negative feedback mechanism	Positive feedback mechanism
• Cause and effect are regulated in an opposite direction. i.e., response decreases the strength of stimulus. • Examples: ✓ ACTH Secretion. ✓ Aldosterone-K⁺ secretion. ✓ Glucose regulation. ✓ GH secretion. ✓ Blood Pressure regulation.	• Stimulus increases the response; The response further intensifies the stimulus strength by a chain reaction. • Also known as 'Vicious cycle'. • Examples: ✓ C-Clotting blood. ✓ -Calcium entry into sarcoplasmic reticulum ✓ L-LH surge during ovulation. ✓ Action potentials(due to Na⁺ gated channels) ✓ S-Shock ✓ P-Parturition

CELL ORGANELLES AND ASSORTED FUNCTIONS:

CELL ORGANELLE	MARKER	FUNCTIONS
Nucleus	• DNA	• Transcription
Mitochondria	• Glutamate Dehydrogenase	• Citric Acid cycle, Oxidative phosphorylation
Ribosome	• RNA	• Site of protein synthesis
Endoplasmic Reticulum	• Glucose-6-phosphatase	• Protein & Lipid synthesis, Oxidation of xenobiotics
Lysosome	• Acid phosphatase	• Site of hydrolases
Plasma Membrane	• Na ⁺ K ⁺ ATPase, • 5'-Nucleotidase	• Molecular transport, Intercellular adhesion & communications
Golgi Apparatus	• Galactosyl transferase	• Sorting of proteins, Glycosylation & Sulfation reactions
Peroxisomes	• Catalase, Uric Acid Oxidase	• Production & degradation of Hydrogen Peroxide,
Cytosol	• Lactate Dehydrogenase	• Glycolysis & Fatty Acid synthesis

CELL MEMBRANE-The Biological Lipid Bilayer

Composition:

- Protein -55%
 - Phospholipids -25%
 - Cholesterol -13%
 - Other lipids -4%
 - Carbohydrate -3%
- NOTE: In almost all the membranes of the body, Proteins are either equal or exceed the quantity of lipids. **The exception is MYELIN (high lipid content provide good insulation)**

CELL MEMBRANE				
Phospholipids			Protein	
○ Along with cholesterol	○ Lipid Rafts	○ Caveolae ○ (Lipid rafts + specific protein Caveolin-1)	○ Integral Proteins ○ (Channels,pumps,carriers)	○ Peripheral proteins
○ Maintains the	○ Involved in signal	○ Involved in signal	○ Transmembrane proteins, Usually globular proteins	○ Present embedded in either the inner or

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fluidity of membrane	transduction	transduction	- Span the lipid bilayer - Asymmetrical distribution. - Amphipathic in nature- Contains both hydrophilic & hydrophobic regions	outer leaflet of the lipid bilayer. * Weakly bound to the hydrophilic region.
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- **The shape of the phospholipid molecule is roughly that of a clothes pin. It is made of two portions:**
 - The HEAD end- PHOSPHATE molecule. (POLAR/HYDROPHILIC)
 - The TAIL end - LIPID molecule. (FAT SOLUBLE/UNPOLAR/HYDROPHOBIC)
 - ✓ In the membrane, the HYDROPHILIC ends are exposed to the aqueous environment on both sides. (ECF side & Cytoplasmic side)
 - ✓ The HYDROPHOBIC ends meet in the water poor interior of the membrane.
- **The membrane is not a solid component. It floats like a gel (fluid mosaic theory!!)**
- **PERMEABILITY OF CELL MEMBRANE :(SELECTIVELY PERMEABLE)**
 - Highly permeable to lipid soluble substances- Oxygen, CO₂, Alcohol
 - Impermeable to water soluble substances like ions, glucose and urea.
 - The order of permeability is:
 - Water > Indole > Urea, Glycerol > Tryptophan > Glucose > Cl⁻ > K⁺ > Na⁺

CYTOSKELETON:

- They are the filamentous structure of the cell which helps in maintaining the cell structure, change in cell shape and its associated functions.

Micro filaments		
○ 7-9.5nm in diameter ○ G-Actin, present in most cells polymerizes to form a double helical F-Actin. ○ F-Actin form microfilaments that exists as bundles of tangled meshwork underlying the plasma membrane ○ Also called as 'Stress fibres'		
Intermediate filaments		
○ 10-12nm in diameter ○ Stable components. ○ In their absence cells rupture easily. ○ Abnormality leads to skin blisters.	Proteins	Distribution
	• Keratins: ○ Type-I (acidic) ○ Type-II (basic)	▪ Epithelial cells, hair ▪ Nails
	• Vimentin	▪ Mesenchyma
	• Desmin	▪ Muscle
	• Glial fibrillary acid protein	▪ Glial cells
	• Peripherin	▪ Neurons
	• Neurofilaments	▪ Neurons
	• Lamins	▪ Nuclear lamina
Microtubules		
○ 25nm in diameter ○ For formation and function of mitotic spindle ○ Involved in Endocytosis & Exocytosis ○ Helpful in axoplasmic transport. ○ Consists of 13 longitudinally arranged protofilaments, consisting of dimers of α and β tubulin. ○ They are in a state of dynamic instability. ○ ASSEMBLY : formed by dimerisation of α and β tubulins (Plus end) ○ DISASSEMBLY: dissociation of α and β tubulins from assembly. (Minus end)	Protein	Function
	○ Dynamin	○ Endocytosis
	○ Kinesin	○ Axonal transport
	○ Cytosolic Dynein	○ Axonal transport
	○ Axonemal Dynein	○ Ciliary flagellar movement

APPLIED PHYSIOLOGY:

- Micro tubule assembly is prevented by Colchicine and Vinblastin.
- Paclitaxel binds to micro tubules & makes them so stable that organelles cant move.

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MOLECULAR MOTORS:

- They are ATPase that moves proteins, organelles and other cell parts from one part to other parts of the cell. Two types:
 - I. Those producing motion along microtubules:
 - DYNEINS:** -moves the material towards the minus end of microtubules.
 - Involved in ciliary & flagellar movement.
 - Defects are implicated in Kartaneger syndrome.
 - KINESINS:** moves the material towards the plus end of microtubules.
 - II. Those producing motion along actin: Myosin I-V

CELL CYCLE:

Stage	Details	Importance
G₀ Phase	• Quiescent cells, Resting phase	• Gene transcription occurs • Non proliferative cells remain in this stage
G₁ Phase	• Pre synthetic phase	• Maximum part of cell cycle • Most variable phase • Growth factors are most effective
S Phase	• DNA synthesis phase	• Increased in malignancy.
G₂ Phase	• Preparation for cell division. DNA repair occurs	• Arrest by P₅₃ gene occurs here.
M Phase	• Mitotic phase	

○ Note:

- G₂ –M phase cells are most susceptible (most radio-sensitive) to radiation injury.
- Cells are most resistant towards the end of S-phase.
- If cells are irradiated in G₁ phase, chromosomal abnormalities may occur.
- If cells are irradiated in G₂ phase, chromatid aberration may occur.

INTERCELLULAR CONNECTIONS:

○ Four kinds of junctions:

- Tight junctions (Zona Occludens)
- Gap junctions
- Desmosomes.
- Hemi desmosomes

Tight Junctions:

- Seal adjacent epithelial cells in a narrow band just beneath their apical surface.
- Functions: Prevent the passage of molecules and ions through the space between cells.
- Proteins forming tight junctions- Occludin, claudin & Junctional Adhesion Molecules (JAMs)
- Block the movement of integral membrane proteins between the apical and basolateral surfaces of the cell.

Gap Junctions: (NEXUS)

- Intercellular channels some 1.5–2 nm in diameter, permit the free passage of ions, glucose and amino acids between the cells but not the proteins.(forming a cytoplasmic tunnel)
- Made of 6 copies of transmembrane proteins called connexins.
- As ions can flow through them, gap junctions permit membrane potential to pass from cell to cell.
- CHARCOT –MARIE TOOTH DISEASE occurs due to a mutation in the gene coding for Connexins.

Desmosomes:

- They are localized patches that hold two cells tightly together, common in epithelia. They are attached to intermediate filaments of keratin in the cytoplasm.

Hemidesmosomes:

- These are similar to desmosomes but attach epithelial cells to the basal lamina instead of to each other.

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BODY FLUID COMPARTMENTS

TOTAL BODY WATER (60% of body weight), 42 liters			
INTRACELLULAR FLUID		EXTRACELLULAR FLUID	
2/3rd of TBW i.e., 40% body weight(28 litres)		1/3rd of TBW i.e., 20% body weight (14 litres)- includes Interstitial fluid, Plasma, Lymph, CSF	
		INTERSTITIAL FLUID	PLASMA
		75% or 3/4th of ECF 15% of body weight (10.5 litres)	25% or 1/4th of ECF 5% of body weight (3.5 litres)

MEASUREMENT OF BODY FLUID COMPARTMENTS

VOLUME	MEASUREMENT
TBW	-By Heavy water (Deuterium oxide), Tritium oxide, Aminopyrine. -By dilution principle
ECF	-Can be called 'SUCROSE SPACE' etc.. -By inulin(most accurate), Sucrose, Mannitol, radio active sodium, radio active chloride, Thiosulfate
PLASMA VOLUME (PV)	-By using Evans blue (T₁₈₂₄), Serum albumin labeled with radioactive Iodine
TOTAL BLOOD VOLUME(TBV)	-Plasma Volume X 100 100-Hematocrit
RED CELL VOLUME	-Volume occupied by all the RBC's. -Determined by TBV-PV -RBCs tagged with radio active Phosphorus, Chromium,Fe
ICF	TBW-ECF(cant be measured directly)

ECF:

- Most abundant cation-Na⁺
- Most abundant anion- Cl⁻

ICF:

- Most abundant cation-K⁺
- Most abundant anion- Proteins> Phosphates
- Thus ECF to ICF ratio will have a high Na⁺ : K⁺ ratio.

- Note: Transcellular fluids**-The fluids inside the cavity. Eg. Synovial fluid, vitreous humor, CSF, pleural, pericardial etc.. (accounts for less than 1litre of TBW)

TRANSPORT ACROSS CELL MEMBRANE:

Passive transport			
- No energy expended by the cell - Goes "downhill" with the gradient - Does not show saturation - Substances move from [HI]→ [LOW]			
Simple diffusion		Facilitated diffusion	
- Solutes move from higher concentration to lower concentration , Random molecular movement - Eg: diffusion of gases in the alveoli		-Carrier protein moves the substance in the direction of their gradient. V_{max} present. - Eg: a. Insulin increases glucose transport in fat & muscle (GLUT) b. Cortisol increases amino acid transport into liver	
Osmosis	Filtration	Bulk flow	Solvent drag
Diffusion of water across a semi-permeable membrane from a solution with lower concentration of solutes to a solution with greater concentration.	Forcing out of fluid through a membrane by a pressure.	- Movement of ions, molecules or particles carried either by fluid or air. - Eg: Movement of air into & out of the lungs, Movement of blood within the vessels.	Water (Solvent) carries dissolved particles with it.

- Simple diffusion occurs through the lipid bilayer or ion channels.**
- Facilitated diffusion occurs through transport proteins.(Carriers)**

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Active transport		
- Requires cell to expend energy - Goes “uphill” or against the gradient - Shows saturation. - Involves embedded proteins (transport proteins) acting like pumps		
Primary active transport (Pumps)	Secondary active transport	Vesicular transport
- The pumps have ATPase. - The energy is derived directly from the break down of ATP. - Eg: a. H^+K^+ pump in parietal cell b. H^+ pump in DCT of nephron c. Na^+K^+ ATPase. d. Ca^{++} pump in Sarcoplasmic reticulum	- Energy gradient generated by a primary active transport is utilized for transport of another substance against gradient. - Eg: • Na^+ - Glucose symport (co transport) • Na^+ - H^+ antiport (counter transport)	Cytopenpsis -Involves Endocytosis & Exocytosis.

Nomenclature of transporters:

Name	Description	Example
Uniport	1 substance is transported	Ca^{++} ATPase, GLUT
Symport (also called Co-transport)	2 substances are transported in the same direction	Na-glucose Co-transport, Na-K-2Cl Co-transport
Antiport (also called Counter transport)	2 substances are transported in the opposite direction	Na^+K^+ ATPase Na^+-H^+ exchanger $Cl^-HCO_3^-$ exchanger

DIFFUSION:

- Fick's law of diffusion:** Diffusion rate (J) = $DA \times dc / dx$
 - ✓ D- Diffusion coefficient, ✓ dc- Concentration gradient
 - ✓ Area available for diffusion ✓ dx- Membrane thickness
- Thus, it is seen that the rate of diffusion is directly proportional to the area, but inversely proportional to the membrane thickness.

OSMOTIC PRESSURE:

- Osmosis is the diffusion of water across a semi-permeable membrane from a solution with lower concentration of solutes to a solution with greater concentration. This continues until osmotic equilibrium is reached.
- OSMOTIC PRESSURE** – pressure which stops osmosis.
 - ✓ Solution with the higher concentration of solutes than plasma is **hypertonic**.
 - ✓ Solution with the lower concentration -**hypotonic**.
 - ✓ Solutions with same concentrations - **isotonic**

Normal serum Osmolality: 300mOsm/kg H_2O. (285-295mOsm/kg H_2O) Plasma Osmolality (mOsm/L) = $2[Na^+] + [glucose]0.055 + [BUN] 0.36$ (mmol/L) (mg/dL) (mg/dL) Or simply, Osmolality = $2[Na^+] + [glucose]/18 + [BUN]/2.8$
BUN-Blood Urea Nitrogen.

- Note:**
 - Plasma Osmolality is mainly due to Na^+ and its accompanying anions.
 - Osmolality is a colligative property and it depends on the number of solute particles rather than the weight contributed by them.
 - Thus, though the plasma proteins have a lower molar mass (weight), they contribute a great to plasma osmotic pressure, as their molar concentration (number) in the plasma is high.

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CHANGES IN VOLUME AND OSMOLARITY FOLLOWING CHANGES IN BODY HYDRATION

CONDITIONS	ECF VOLUME	OSMOLARITY	ICF VOLUME
○ Loss of isotonic fluid: ○ (Hemorrhage, Diarrhea, Vomiting)	↓	No Change	No Change
○ Loss of hypotonic fluid: ○ (Dehydration, Diabetes Insipidus, Alcoholism)	↓	↑	↓
○ Gain of isotonic fluid: ○ (Isotonic saline infusion)	↑	No Change	No Change
○ Gain of hypotonic fluid: ○ (Hypotonic saline infusion, Water intoxication)	↑	↓	↑
○ Gain of hypertonic fluid: ○ (Hypertonic saline, Hypertonic mannitol infusion)	↑	↑	↓

- **DEHYDRATION:** ECF Volume contraction **OVERHYDRATION:** ECF Volume expansion

Classification of dehydration:

Type	Example
○ Iso osmotic	○ Blood loss
○ Hyper osmotic	○ Vasopressin insufficiency
○ Hypo osmotic	○ Adrenal insufficiency

- **Some Isotonic solutions:**

- 0.85% NaCl
- 5% dextrose*
- 20% Urea
- 10% Mannitol

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- 5% dextrose contains 50g of dextrose per liter of solution. Its molar mass=180g. So, its Osmolality= 50/180 mol =0.277 mol or 277mOsm.
- Hence it is an **ISOSMOTIC** solution. But when it is infused, dextrose gets metabolized and only the water stays in the plasma. Thus the solution becomes **HYPOTONIC**.
- NOTE:** Hemolysis begins when RBC's are placed in 0.5% NaCl and is complete in 0.3% NaCl. (Osmotic fragility!!)

VESICULAR TRANSPORT

	EXOCYTOSIS		ENDOCYTOSIS	
Defn.	- Process by which substances are expelled from the cell. - Requires Ca^{2+} and energy		- Process by which substances enter the cell. - Requires Ca^{2+}, contractile elements and energy	
Mechanism	- Inner membrane of the vesicle fuses with the outer membrane. - Cytoplasmic side of the vesicle fuses with Cytoplasmic side of the plasma membrane.		- Two non Cytoplasmic side of membranes fuse. - Lead to removal of cell membrane, thus preventing the cell from enlarging and thus maintaining the surface area of the cell.	
Types	Secretion from the cell occurs in two ways		PHAGOCYTOSIS ‘Cell eating’	PINOCYTOSIS ‘Cell drinking’
	CONSTITUTIVE	NON CONSTITUTIVE	✓ Occurs only in specialized cells like macrophage & granulocyte ✓ Involves ingestion of viruses, bacteria etc..	Fluid phase ✓ Is a non selective process. the uptake of solute is proportionate to its concentration Absorptive ✓ Receptor mediated selective process. ✓ responsible for uptake of macro molecules
	✓ Prompt transport of proteins to cell membrane in vesicles with no processing.	✓ Also called regulated pathway ✓ Proteins are processed in the Golgi apparatus before being expelled.		

Points of Special mention:

- EMEIOCYTOSIS:** Reverse pinocytosis.
 - Type of Exocytosis responsible for insulin secretion.
 - Promoted by Ca^{2+} , K^{+}
 - Inhibited by Mg^{2+}
- TRANSCYTOSIS/ CYTOPEMPSIS:**
 - Small amount of proteins are transported out of capillaries across endothelial cells by endocytosis on the capillary side followed by exocytosis on the interstitial side of the cells.
- Receptor mediated Endocytosis:**
 - Clathrin - internalization of LDL, NGF
 - Caveolin-Cellular digestion of various vitamins

Mechanism of actions of chemical messengers in the ECF

Mechanism	Examples
Open or close ion channels in cell membrane	Ach on cholinergic receptor, nor adrenaline on K^{+} channel in the heart
Act via cytoplasmic/ nuclear receptors to increase transcription of selected mRNAs	Thyroid hormones, retinoic acid, steroid hormones
Activate phospholipase C with intra cellular production of DAG, IP3 & other inositol phosphates	Angiotensin-II, Nor adrenaline via $\alpha 1$ – adrenergic receptor, vasopressin via V_1 receptors.

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○ Activate or inhibit adenylyl cyclase, causing increased or decreased intracellular production of Camp	○ Nor adrenaline via β_1 – adrenergic receptor, Nor adrenaline via α_2 – adrenergic receptor,
○ Increase cGMP in cell	○ ANP, nitric oxide
○ Increase tyrosine kinase activity of transmembrane receptors	○ Insulin, epidermal growth factor, platelet derived growth factor, monocyte colony stimulating factor
○ Increase serine or threonine kinase activity	○ TGF- β , activin, inhibin

Examples of disorders due to abnormalities caused by loss or gain of function mutations of heterotrimeric G protein coupled receptors and G proteins

Receptor	Type of mutation	Disease
Cone opsins	• Loss	• Color blindness
Rhodopsin	• Loss	• congenital night blindness, two forms of retinitis pigmentosa
V2 vasopressin	• Loss	• X- linked nephrogenic diabetes insipidus
ACTH	• Loss	• Familial gluco corticoid deficiency
LH	• Gain	• Familial male precocious puberty
TSH	• Loss	• Familial hypothyroidism
TSH	• Gain	• Familial non auto immune hyper thyroidism
Ca ²⁺	• Gain	• Familial hypercalciuric hypocalcemia
Thromboxane A 2	• Loss	• Congenital bleeding
Endothelin B	• Loss	• Hirschsprung disease
G-protein	Type of mutation	Disease
G _s α	✓ Loss	✓ Pseudohypothyroidism type-1a
G _s α	✓ Loss/ gain	✓ Testotoxicosis
G _s α	✓ Gain	✓ McCune Albright syndrome
G _s α	✓ Gain	✓ Somatotroph adenomas with acromegaly
G _i α	✓ Gain	✓ Ovarian and adreno cortical tumors

ELECTROPHYSIOLOGY

MEMBRANE CONDUCTANCE:

- Alteration of membrane conductance leads to change in membrane potential.
- Channels are classified into three main groups:

Ungated channels	Voltage gated channels	Ligand gated channels
○ Always open ○ Eg: All cells possess ungated K⁺ channels. ○ This means that there will be a net influx of K⁺ ions through this channels unless K⁺ is at equilibrium.	○ The gates open/close in response to a membrane voltage change. ○ Eg: Voltage gated Na⁺ channels. ○ They are closed during resting state but membrane depolarization causes them to quickly open and then to close.	○ The channel has a receptor to a specific ligand or chemical. ○ Interaction of the ligand with the receptor regulates the opening & Closing of the channel. ○ Eg: Acetyl Choline mediated channels .

RESTING MEMBRANE POTENTIAL (RMP):

- It is the potential difference existing across the membranes when the cell is in the resting state. (Unexcited state).
 1. In a resting state the **membrane is 100 times more leaky to K⁺ than Na⁺**. So, the K⁺ ions exit from the cell down its concentration gradient. (from ICF to ECF). The exit of positively charged K⁺ ions leaves negatively charged ions inside the cell membrane.

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2. The **cell membrane is totally impermeable to organic anions** and proteins present in the ICF.
3. The $\text{Na}^+\text{K}^+\text{ATPase}$ pump, which is electrogenic, pumps out 3 Na^+ to the ECF but it pumps in only 2 K^+ ions, thus it makes the interior of the cell negative with respect to the exterior. Hence a potential difference exists across the CM which is negative on the interior.
- This is measured by placing two electrodes, one over the membrane & the other in the interior of the cell. The ratio of intra cellular to extra cellular K^+ concentration (normally 38:1) is the crucial factor in maintaining the RMP and vital for neuro muscular function.

RMP of different tissues:

Cell/tissue	RMP(inside negative)
○ Skeletal muscle	○ -90 mV
○ Cardiac muscle	○ -90mV
○ SA Node	○ -70mV
○ GI smooth muscle	○ Variable, -40 to -60 mV
○ Nerve cells	○ -70mV
○ RBC's	○ -10mV

Non ionic diffusion:

- Some ions and bases are quite soluble in cell membranes in the undissociated form, whereas they cannot cross in the charged (dissociated) form.
- If molecules of the undissociated substance diffuse from one side of the membrane to the other and then dissociate, there is appreciable net movement of the undissociated substance from one side of the membrane to the other.
- Eg. The process by which NH_3 is secreted into the urine & then changed to NH_4^+ , maintaining the concentration gradient for diffusion of NH_3 .

Gibbs Donnan Effect:

- The negatively charged proteins and phosphates which are present inside the cell cannot diffuse across the membrane. This results in a greater permeability of chloride (a diffusible anion). This is called Gibbs Donnan Effect.

Equilibrium Potential:

The membrane potential at which there is no net flux of a particular ion.

It is the electrical potential which balances the flux due to chemical gradient. This equilibrium potential is calculated using **NERNST EQUATION**.

Concentration of ions (mmol/L):

Ion	ICF	ECF	Equilibrium potential(mV)
Na^+	10	140	+60
K^+	140	5	-90
H^+	13×10^{-5}	3.8×10^{-5}	-32
Cl^-	10	120	-70
HCO_3^-	8	27	-32
Proteins	155	0	--

Membrane Potential= -90mV

- Eg: Na^+ influx will stop when the membrane potential reaches +60mV. This means that the equilibrium potential for Na^+ is +60 mV.
- Equilibrium potential for Na^+ (E_{Na}): $-61 \log [\text{Na}_i]/[\text{Na}_o]$

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$$= -61 \log 10/140$$

$$= +61 \text{ mV.}$$

- **Use of Nernst Equation:** to calculate the ion's equilibrium potential at a given concentration gradient.

Role of ions in maintaining the electrical activity of the cell:

K ⁺ ion	Na ⁺ ion	Cl ⁻ ion
• Potassium leak channels have a role in genesis of RMP. • Increasing the potassium conductance will cause K⁺ efflux and repolarisation. • Hyperkalemia: leads to decreased K⁺ efflux or even create an influx, the net result will be depolarization. • Hypokalemia: ✓ leads to K⁺ efflux, resulting in ✓ Hyperpolarization. ✓ Thus the cell's RMP is very sensitive to ECF K⁺ ion concentration.	• Sodium channels are less leaky than potassium leak channels at rest. • An increase in membrane conductance to sodium ions will lead to Na⁺ influx resulting in depolarization. • As the Na⁺ channels are closed at rest, changes in ECF sodium will not affect the RMP.	• As the measured membrane potential and the calculated equilibrium potential for Cl⁻ are the same in magnitude and charge, the chloride ions are at equilibrium. • Any change in the membrane conductance of chloride ions will not cause a net diffusion of chloride ions.

Some definitions:

- **Depolarization:** (loss of polarity or loss of negativity of the interior) the negative intracellular potential moves towards zero. (becomes more positive) e.g., Na⁺ influx depolarizes a cell.
- **Repolarization:** returning back to RMP.
- **Hyperpolarisation:** The negative intra cellular potential becomes more negative. e.g., continued K⁺ efflux from a cell.

ACTION POTENTIAL

- The sequence of changes that take place in the membrane potential when a threshold stimulus is applied following its restoration to the resting level is called **action potential**.
- *The neuron is at **resting membrane potential** which is around -70 mv (inside of the neuron is negative compared to outside).

Part of action potential	Feature
○ Depolarization	• Na ⁺ influx
○ Firing level	• After initial 15mV of depolarization, (once it reaches the threshold) the rate increases. This is firing level.
○ Upstroke phase	• Rapid depolarization phase caused by rapid Na ⁺ influx
○ Overshoot	• Part of action potential during which the membrane potential is positive.
○ Repolarization or down stroke phase	• Rapid return of membrane towards RMP. It is due to a. Closing of Na⁺ channels b. Opening of K⁺ channels
○ Undershoot or hyperpolarisation	• Membrane potential becomes more negative than its initial RMP. It is due to leaky potassium channels.

PROPERTIES OF ACTION POTENTIAL:

- **Threshold stimulus:** The minimal stimulus intensity that will elicit an action potential in an excitable tissue. Stimulus: can be electrical, chemical or mechanical.
 - Sub threshold stimulus - No response.
 - Threshold/Liminal stimulus - Action potential
 - Supra threshold - No further increase in action potential (**all or none law**)

Refractory period:

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Absolute refractory period	Relative refractory period
- Is a period during which no matter how strong the stimulus, it cannot induce a second action potential. - due to inactivation of Na^+ channels - Correspond to period from time the firing level is reached until repolarisation is $1/3^{\text{rd}}$ complete.	- It is the period during which a stronger than normal stimulus can induce a second action potential. - Correspond to period from the end of ARP to start of hyperpolarisation.

$\text{Na}^+ \text{K}^+$ ATPase pump:

- The $\text{Na}^+ \text{K}^+$ ATPase pump, which is electrogenic, pumps out 3 Na^+ to the ECF but it pumps in only 2 K^+ ions, thus it makes the interior of the cell negative with respect to the exterior.
- A primary active transport process present in all cells (Ubiquitous), in the cell membrane.
- Plays an important role in maintaining the cell volume. If the pump is inhibited, intracellular sodium accumulation occurs leading to increase in cell size & cell rupture.
- Digoxin inhibits the pump.
- About 70% of the ATP generated in the body is used to energize the pump.

Structure:

- Made up of α and β subunits.
- The α subunit transports 3 Na^+ ions out of the cell but it pumps in only 2 K^+ ions for each molecule of ATP hydrolyzed.
- The pump is facilitated by thyroid hormones, Aldosterone and Insulin and inhibited by dopamine in the kidney leading to natriuresis.

EXCITABLE TISSUE- MUSCLE AND NERVE

- NUMBER OF NEURONS IN CNS: 10^{11}
- NUMBER OF CELLS IN NEUROGLIA: 10^{12}
- NUMBER OF SYNAPSES: 10^{13}
- NUMBER OF SYNAPSES > NEUROGLIA > NEURONS
- Types of neuron:**
 - Multipolar Neuron:** 1 axon and multiple dendrites attached to the soma & Most common type of neuron found in the CNS
 - Bipolar Neuron:** 1 axon and 1 dendrite located at opposite ends of the soma & Usually sensory neurons
 - Unipolar Neuron:** 1 axon attached to the soma. Axon divides, with one branch receiving sensory information and the other sending the info into the CNS
- Golgi-type-I neurons: neurons with long axons
- Golgi-type-II neurons: neurons with short axons

NEUROGLIA:

- Microglia:** scavenger cells of CNS, variant of macrophages.
- Macroglia:** 3 types

Oligo dendrocytes	Schwann cells	Astrocytes
Myelin formation in Central NS	Myelin formation in Peripheral NS	Formation of BBB. Fibrous Astrocytes: - contain intermediate filaments, found in white matter Protoplasmic Astrocytes: found in gray matter

MYELINATION:

- PNS:**
 - Schwann cell wraps its membrane around an axon up to 100 times, except at the nodes of Ranvier.
 - The myelin is then compacted by locking of a protein called P_0 (protein zero) with the opposing membrane.

DMA'S CORNER OF WISDOM

- Schwann cell forms myelin around a single neuron in between two nodes.
- In unmyelinated neurons, the axons are simply surrounded by Schwann cells.
- CNS: Oligo dendrocytes emit multiple processes that form myelin on many neighboring neurons.

Multiple sclerosis:

- Multiple sclerosis is a crippling auto immune disease associated with patchy destruction of myelin sheath.
- Environmental triggers include EBV, Measles, Chicken pox, herpes and influenza.
- Loss of myelin leads to leakage of K^+ through voltage gated channels, hyper polarization and failure of conduction of impulses.
- Nerve conduction tests: slowed conduction in motor & sensory pathways.
- CSF analysis: presence of oligoclonal bands indicative of an abnormal immune reaction against myelin.
- Most definite investigation: MRI- multiple scarred areas in the brain.

Axoplasmic transport:

- Fast anterograde transport from the cell bodies to axon terminals along micro-tubules.

Axoplasmic transport	Velocity of conduction
• Fast anterograde transport (kinesin mediated)	• 400mm/day
• Slow anterograde transport	• 0.5-10mm/day
• Retrograde transport(dynein mediated)	• 200mm/day

- Anterograde transport , transports cytoplasmic materials & proteins synthesized in the cell body to the axon terminals
- Retrograde transport includes transport of neurotropic viruses like polio, rabies & HSV, tetanus toxins & some Neurotrophins from the axon terminal towards the cell body.

CLASSIFICATION OF NERVE FIBRES :(Erlanger & Gasser classification)

Fiber type	Function	Diameter (μm)	Conduction velocity (m/s)	Absolute refractory period(ms)	Most susceptible to
A α	Proprioception, somatic motor	12-20	70-120	0.4-1	Pressure
β	Touch, pressure, motor	5-12	30-70		
γ	Motor to muscle spindles	3-6	15-30		
δ	Pain ,cold, touch	2-5	12-30		
B	Pre ganglionic autonomic	<3	3-15	1.2	Hypoxia
C Dorsal root	Pain, temperature, reflex responses	0.4-1.2	0.5-2	2	Local anesthetics
Sympathetic	Post ganglionic sympathetic	0.3-1.3	0.7-2.3	2	

Features:

- A & B are myelinated while **C fibres are unmyelinated**.
- Greater the diameter of the fibre, greater will be the speed of conduction.
- **Large axons** for: -conscious touch & pressure, somatic motor function & proprioceptive sensation
- **Small axons** for – pain, temperature & visceral functions
- **Touch** is carried by **Aβ & Aδ** fibres while **Pain** is carried by **Aδ & C** fibres.

NUMERICAL CLASSIFICATION FOR SENSORY NEURONS:

NUMBER	ORIGIN	FIBER TYPE
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Ia	• Muscle spindle, annulo-spiral ending	• Aα
Ib	• Golgi tendon organ	• Aα
II	• Muscle spindle, flower spray ending, touch, pressure	• Aβ
III	• Pain & Cold receptors, Some touch receptors	• Aδ
IV	• Pain, temperature & other receptors	• Dorsal root C

NERVE INJURY (Seddon's classification):

- **Neuropraxia:** functional disruption of conduction, no degeneration, complete recovery
- **Axontemesis:** disrupted axons with intact sheath, degeneration occurs, good prognosis
- **Neurontemesis:** complete division of nerve, degeneration occurs, poor prognosis
- **Tinel's sign is absent in neuropraxia.**

Changes in nerve fibers after injury:

- Ante grade degeneration: - degeneration of the distal part (**Wallerian degeneration**)
- Retro grade degeneration: -occurs up to the proximal node of Ranvier.
- Regeneration: completed in 80 days
- **First change** in cut nerve: **Axonal degeneration**, followed by Myelin degeneration.

ACTION POTENTIAL IN A NERVE FIBER:

- develops in the initial segment of a spinal motor neuron.
- develops in the first node of Ranvier in cutaneous sensory neuron.
- follows **all or none** phenomenon.
- Saltatory conduction (jumping conduction) is seen in myelinated fibers.
- Axons can conduct nerve impulses in either direction but synapses permit conduction in one direction only. i.e., **PRESYNAPTIC → POST SYNAPTIC NEURON.**

SYNAPSE

- Junctions where the axon of one nerve cell terminates on the dendrites, soma or axon of other neuron.
- **TYPES:** - **Axo dendritic** (most common), axo-axonal, axo-somatic.
- **Synaptic delay: 0.5ms**
- **Synaptic proteins:**
 - **V-snare protein:** Synaptobrevin, in vesicle membrane. Tetanus toxin, botulinum toxins B, D, F, & G act on it.
 - **T-snare protein:** Syntaxin, in cell membrane. Botulinum toxin C acts on it.
 - **SNAP-25:** botulinum toxins A & B act on it.
- Tetanus toxin- Spastic paralysis by blocking presynaptic transmitter release in CNS
- Botulism- Flaccid paralysis by blocking Ach release in the NMJ.
- **ELECTRICAL EVENTS IN POST SYNAPTIC NEURONS:**
 - **EPSP:** Depolarization of the post synaptic membrane-Opening of Na⁺ or Ca²⁺ channels, producing an inward current
 - **IPSP:** Hyperpolarisation of the post synaptic membrane-Opening of Cl⁻ or K⁺ channels

SYNAPTIC INHIBITION:

Pre-synaptic(indirect) inhibition	Post synaptic (direct/reciprocal)inhibition
○ -failure of presynaptic neuron to release the excitatory neurotransmitter.	○ - Due to release of an inhibitory neurotransmitter.

Special types of direct inhibition:

- **Renshaw Cell Inhibition:** negative feedback inhibition of a spinal motor neuron by an inhibitory interneuron. (Renshaw cell).
- **Feed Forward Inhibition:** seen in the cerebellum,

DMA'S CORNER OF WISDOM

FACTORS AFFECTING NERVE GROWTH (Neurotrophins)

- -produced by astrocytes and also by the muscles which the neurons innervate.
- **Nerve Growth Factor (NGF)** - first neurotrophin to be identified. It has insulin like activity.
- **Neurotrophins:**
 - Proteins necessary for survival & functions of neurons.
 - Four Neurotrophins are identified and their high affinity receptors are the trk receptors which on dimerisation initiates auto Phosphorylation in the cytoplasmic tyrosine kinase domains of the receptors.
 - The first neurotrophin to be identified was nerve growth factor (NGF), which has an additional low affinity receptor called p75^{NTR}.

Neurotrophin	Receptor
○ Nerve Growth Factor (NGF)	○ trk A
○ brain derived neuro tropic factor (BDNF)	○ trk B
○ Neurotrophin 3 (NT 3)	○ trk C, to lesser extent trk A & trk B
○ Neurotrophin 4/5 (NT-4/5)	○ trk B

RULES IN NERVOUS TRANSMISSION:

- **Bell Magentie law:** in spinal cord- Dorsal roots are sensory & ventral roots are motor.
- **Weber-Fechner law:** Magnitude of sensation felt is proportionate to the log of intensity of the stimulus.
- **Law of projection:** no matter where a particular sensory pathway is stimulated along its course to the cortex, the conscious sensation produced is referred to the location of the receptors.
- **Muller's Doctrine of specific nerve energies:** when the nerve pathways from particular sense organs are stimulated, the sensation evoked is that for which the receptor is specialized no matter how or where along the pathway the activity is initiated.

STRUCTURE OF SKELETAL MUSCLE:

- Muscle → Muscle fibres → Myo filaments → contractile proteins.
- **The contractile proteins are:**
- Myosin-II, Actin, tropomyosin, Troponin (Trop-I/Trop-T/Trop-C)
- **The filaments are of two types (thick & thin)**
 - **THICK-** made of Myosin-II proteins (single head & two tails. The head contains ATPase activity). Each myosin filament is surrounded by six actin filaments.
 - **THIN-** made of ACTIN, TROPONIN & TROPOMYOSIN.
 - ✓ **ACTIN:** has binding sites for ATP, myosin & Troponin.
 - ✓ **TROPONIN:** has 3 sub units-I, T, C.
 - **TROP-I:** Binds with Actin & inhibits its interaction with myosin
 - **TROP-C:** binds with Ca²⁺ & shifts the Tropomyosin molecule from the active site of Actin & allows myosin to bind with it.
 - **TROP-T:** binds other Troponin to Tropomyosin.
 - ✓ **TROPOMYOSIN:** covers the active site of actin.

MUSCLE HISTOLOGY:

- **Z line:** divides each myofibril into compartments. e portion of myofibril between two Z line is a sarcomere.
- **I band:** formed by thin filament mainly actin. ; **A band:** overlapping of actin & myosin
- **H zone:** narrow lighter area at the middle of A band, no actin in this zone.
- **M line:** transverse line in the middle of H zone.
- Myosin & actin gets linked by cross bridges. Top of cross bridge is formed by myosin head & it has sites for attachment of actin & ATP.
- → **Nebulin, Connectin, Actinin, Titin, Dystrophin** -other proteins that help in Sk. Muscle contraction

IN A CONTRACTED STATE:

- **H zone** is greatly narrowed & disappears
- **Width of I band** is reduced.

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- Width of **A band** remains **unchanged**.
- **Z line** moves closer
- The muscle fibre as whole shortens

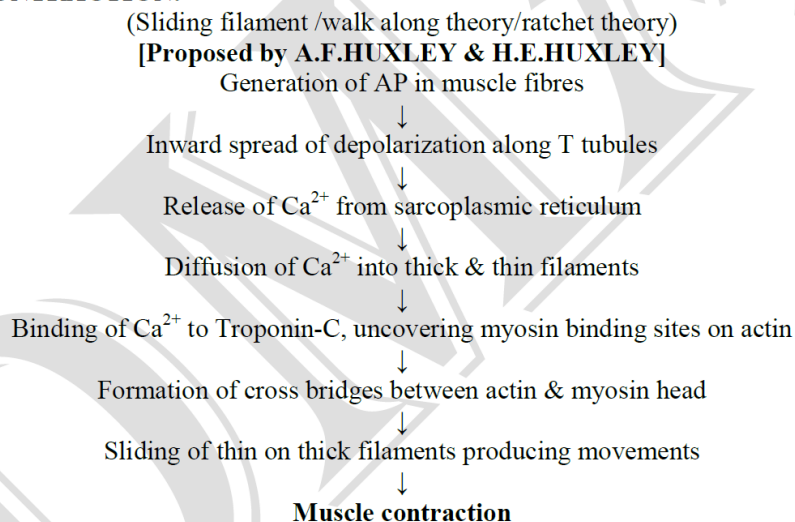
SARCO-TUBULAR SYSTEM:

- **'T' (transverse) tubules:** penetrate the muscle cells & opens to the ECF: responsible for **rapid transmission** of AP.
- **'L' (longitudinal) tubules:** extends throughout the sarcoplasm, no connection to the exterior: **storage house** of Ca^{2+}

Two types of receptors in muscle contraction:

- **Dihydro-pyridine receptors (DHPR)** are the voltage gated Ca^{2+} channels in T-tubules of cardiac muscle, influx of Ca^{2+} via these channels triggers the release of Ca^{2+} stored in the SR via **Ryanodine(RYR) receptors**. [calcium induced calcium release]
- In the skeletal muscle, DHPR serves merely as voltage sensor & unlocks release of Ca^{2+} from the nearby RYR receptor via physical interaction.
- Thus, **main source of Ca^{2+} for contraction in:** Skeletal muscle-SR: Cardiac muscle-ECF

MECHANISM OF CONTRACTION:



RELAXATION:

- The SERCA pump Sarcoplasmic or Endoplasmic Reticulum Ca^{2+} ATPase pumps the calcium back to sarcoplasmic reticulum.

Role of calcium in Excitation contraction coupling	
Smooth muscle	Skeletal/cardiac muscle
• AP → Ca^{2+} release → Ca^{2+} binds to calmodulin → activates MLCK → phosphorylates myosin • Myosin phosphorylation-crucial factor for contraction • Troponin is not essential. • Sustained contraction- produced by latch bridge mechanism. The myosin cross bridges remain attached to actin for sometime after cytoplasmic Ca^{2+} falls	• Ca^{2+} ions initiate the process of contraction by binding with Troponin-C → uncovers myosin binding sites on actin → actin attaches to myosin → contraction.

CALCIUM RELATED PROTEINS:

- **Calsequestrin-** for sequestration of calcium.

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- **Calmodulin**- Ca^{2+} binding protein, counter part of Troponin present in smooth muscles,
 - Binding of Ca^{2+} & calmodulin activates MLCK (Myosin Light Chain Kinase)
- **Calcineurin**- calmodulin activated protein, inactivates Ca^{2+} channels by dephosphorylation.
- **Calcium binding proteins**: troponin, calmodulin, calbindin
- ATP provides energy for both muscle contraction (at the myosin head) and relaxation (SERCA pump).
- If transport of Ca^{2+} into the reticulum is inhibited, relaxation does not occur even though there are no more action potentials; the resulting sustained contraction is called **contracture**.

PROPERTIES OF MUSCULAR CONTRACTION:

1. Contraction cycle

- Muscles can not push; they may only CONTRACT (pull)
- a single muscle contraction is called a muscle TWITCH

parts of a Muscle twitch [CONTRACTION CYCLE]	
◦ Latent period - 5 m sec	◦ time between application of AP & initiation of contraction
◦ Contraction - 40 m sec	◦ muscle shortens & does its work
◦ Relaxation - 50 m sec	◦ Muscle elongates & returns to original position
◦ Refractory period - 2msec	◦ time of recovery between stimulations of muscle

2. **Tetanus** - at higher frequency of stimulation muscle relaxation between contractions is reduced. It may be complete or incomplete.

3. **Treppe – Stair Case Phenomenon**: relaxation is complete before next stimulus occurs; each contraction is a little stronger than previous. Physiological efficiency improves because of gradual increase in Ca^{2+} in sarcoplasm. Basis for warm-up.

4. Tension:

- **TOTAL TENSION**: tension that a muscle develops when contract isometrically.
- **PASSIVE TENSION**: tension exerted by the unstimulated muscle.
- **ACTIVE TENSION**: tension generated by the contractile process.
- **Resting length**: length of the muscle at which the active tension is maximal

5. Heat produced in a muscle:

- **RESTING HEAT**- heat given off at rest
- **ACTIVATION HEAT**- heat produced by muscle during contraction (mainly due to Ca^{2+})
- **INITIAL HEAT**- heat produced in excess of resting heat during contraction.
- **SHORTENING HEAT**- heat produced by muscle shortening
- **RECOVERY HEAT**- heat liberated by the metabolic process to restore the muscle to pre contraction state.
- **Fenn effect**: heat produced is directly proportional to the work done by the muscle.

TYPES OF SKELETAL MUSCLE CONTRACTION:

Isotonic contraction	Isometric contraction
◦ Constant tension, muscle shortens	◦ Tension increases, muscle does not shorten
◦ Contraction against a constant load with a decrease in muscle length.	◦ Contraction without decrease in the muscle length.
◦ External work is done	◦ No work done
◦ Eg. Walking, running	◦ Eg. Lifting heavy weight, sustained hand grip

CLASSIFICATION OF SKELETAL MUSCLE FIBERS:

	Type-I	Type-IIA	Type-IIB
Other names	Slow, Oxidative	Fast, oxidative, glycolytic	Fast, glycolytic
Colour	Red	Red	White
Myosin ATPase activity	Slow	Fast	Fast
Ca^{2+} pumping capacity of SR	Moderate	High	High
Diameter	Small	Large	Large
Glycolytic capacity	Moderate	High	High

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DMA'S CORNER OF WISDOM

Oxidative capacity	High	Moderate	Low
Fatigability	Slow	Fast	Very fast

COMPARATIVE PROPERTIES OF SKELETAL, CARDIAC AND SMOOTH MUSCLE

Properties	Skeletal muscle	Cardiac muscle	Smooth muscle
HISTOLOGY	- Striated - No intercellular coupling	- Striated - Syncytium +	- Non striated - Syncytium +
Sarcomeres	Well organized	Well organized	Absent
RMP	-90mv	-90mv(ventricles) -55mv(S.A Node)	Variable, -50mv
Duration of AP	2-5 ms	250-400 ms	Variable
Refractory period	Short	Long	Short
Twitch duration	50-100ms	800ms(varies with HR)	Long tonus
Summation	Yes	No	Yes
Tetanus	Possible	Impossible	Possible
Source of Ca²⁺	From SR	ECF	Mainly from ECF
Regulatory proteins	Troponin -C & Actin	Troponin-C	Calmodulin & Myosin
Length tension relationship	Linear	Linear	Non-linear
Metabolism	Aerobic & anaerobic glycolysis	Aerobic	Aerobic
Myosin ATPase rate	Fast	Slow	Slowest

Smooth muscle Types:

- Single unit – Mass of hundred to thousands of smooth muscle fibres contract together as single unit; electrically coupled (gap junctions); some are spontaneous.
- Multunit – made of individual fibers without inter connecting bridges. Occur in large airways and arteries, erector pili and ciliary muscles of the eye.
- Synapse en passant:** neuron forms a synapse on the other neuron or a smooth muscle cell & then passes on to make similar contacts with other cells.

MUSCLE METABOLISM

- Immediate source of energy: ATP.
- Source of ATP:**
 - First source: muscle creatine
 - Second source: glycogen
 - Third/ ultimate source: oxidative phosphorylation

OXYGEN DEBT

- After exercise:
 - ✓ the body needs more oxygen than usual to normalize metabolic activities
 - ✓ resulting in heavy breathing

MUSCLE PATHOLOGIES

- Myasthenia gravis**
 - Autoimmune disease which involves neuromuscular junction characterized by impaired neural impulse transmission.
- Duchene's muscular dystrophy**

DMA'S CORNER OF WISDOM

- Most common MD is deficiency of dystrophin, an integral plasma membrane protein that links various structural proteins to membrane. Associated with degeneration of skeletal muscle
- **Myotonic dystrophy**
 - Genetic muscle disease associated with extreme muscle wasting
- **Myositis**
 - Inflammatory muscle diseases (infectious and immune)
- **Poliomyelitis**
 - Infectious disease causing muscle weakness
- **Amyotrophic lateral sclerosis**
 - Neurological disease that attacks neurons for controlling voluntary muscles
- **Cerebral palsy**
 - Neurological disorders that appear in infancy and permanently affect muscle coordination and body movement
- **Rigor mortis**
 - -depletion of ATPs after death. The cross bridges cannot detach from actin.
- **Lambert- Eaton Syndrome:**
 - muscle weakness due to auto-immune attack against one of the calcium channels in the nerve endings of NMJ

CENTRAL NERVOUS SYSTEM AND SPECIAL SENSES

ORGANISATION OF THE BRAIN

FORE BRAIN:

- **TELENCEPHALON**-Cerebral hemispheres, lobes, cortex & subcortical nuclei.
 - 2 Hemispheres connected by commissures(Corpus callosum being the largest)
 - Basal ganglia is the predominant subcortical nuclei.
- **DIENCEPHALON**- upper 2/3rd [Thalamus] & lower 1/3rd [Hypothalamus]

MIDBRAIN: [MESENCEPHALON]

- **VENTRAL PART: CEREBRAL PEDUNCLE**, Made mainly of white matter, unites the Pons with thalamus. Comprises of tegmentum, substantia nigra and basis peduncle.
- **DORSAL PART: TECTUM**, comprises two elevations – superior & inferior colliculi.

HIND BRAIN: [RHOMBENCEPHALON]

- Comprises of Pons, Medulla and Cerebellum.

Note:

- The cerebellar peduncles connect the cerebellum with the dorsal side of the brain stem via:
 - Superior C.P→ with midbrain
 - Middle C.P→ with Pons
 - Inferior C.P→ with medulla.
- Limbic system- formed by both grey & white matter.

STRUCTURE OF SPINALCORD: [C/S]:

- **Grey matter**- consists of nerve cells- forms anterior & posterior horns;
 - **Ventral/anterior horn**: contains cell bodies of α , γ and Renshaw cell motor neurons. Axons of α and γ motor neurons pass out in anterior roots.
 - **Dorsal/Posterior horn**: purely sensory.
- **White matter**- consists of anterior, lateral& posterior white columns.

RECEPTORS

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DMA'S CORNER OF WISDOM

- Specialized modified sensory nerve ending which undergoes depolarization in response to specific stimuli & in turn sends information to CNS.
- **TYPES:**
 - A. Sherrington's classification:**
 - i. Telereceptors- concerned with sensory perception at a distance. E.g.: hearing, vision, smell
 - ii. Exteroceptors- concerned with perception of external stimuli. E.g.: touch, pressure, temperature, pain etc...
 - iii. Interoceptors: respond to changes of the internal environment.
 - A. Proprioceptors: information about changes in position of the body in space. Includes muscle spindles, joint receptors, Golgi tendon organs & Vestibular receptors.
 - B. Visceroceptors: Baroreceptors, Osmoreceptors and glucoreceptors.
 - C. Chemoreceptors.
 - B. Anatomical classification:**
 - i. Special senses- located in head
 - ii. Superficial or cutaneous senses
 - iii. Deep senses
 - iv. Visceral senses.

MODALITY	STIMULUS	RECEPTOR CELL TYPES
Touch	• Tap, flutter	• Meissner's corpuscles
	• Motion	• Hair follicle receptors
	• Deep pressure, vibration	• Pacinian corpuscles
	• Touch, pressure	• Merkel cells
	• Sustained pressure	• Ruffini corpuscles
Proprioception	• Stretch	• Muscle spindles
	• Tension	• Golgi tendon organ
Temperature	• Cold	
	• Warm	
Balance	• Angular acceleration	• Hair cells (semi circular canals)
	• Linear acceleration	• Hair cells (otolith organs)

ADAPTATION:

- When a maintained stimulus of constant strength is applied to a receptor, the frequency of action potentials in its sensory nerve declines over time. **This is known as adaptation/ desensitization.**
- Receptors can be classified as rapidly adapting (phasic) receptors and slowly adapting (tonic) receptors.
- **Rapidly adapting receptors:** Meissner and Pacinian corpuscles,
- **Slowly adapting receptors:** Merkel cells, Ruffini endings, muscle spindles, nociceptors.

Thermal receptors

- The receptor for moderate cold is the **cold and menthol sensitive receptor-1 [CMR-1]**
- Two types of vanilloid receptors respond to noxious heat [VR-1 & VRL-1]. Vanillins are pain producing substances. Eg. Capsaicin.
 - a. VR 1 receptors respond not only to capsaicin but also to protons and to potentially harmful temperatures above 43°C.
 - b. VRL-1 which responds to temperatures above 50°C but not to capsaicin has been isolated from C fibers.
 - c. There may be many types of receptors on single peripheral C fiber endings, so single fibres can respond to many different noxious stimuli.
- All the 3 receptors CMR-1, VR-1 & VRL-1 are members of the transient receptor potential (TRP) family of excitatory ion channels.

DMA'S CORNER OF WISDOM

REFLEXES

MUSCLE SPINDLE:

- Each muscle spindle consists of 10 muscle fibres enclosed in a capsule.
- The fibres inside the spindle are called **intra fusar**, while those outside are **extra fusar**.
- The intra fusar fibres are of two types: -Nuclear bag fibres -Nuclear chain fibres
- Two types of sensory nerve endings in each spindle:
 - ✓ Primary (**annulo spiral**) ending: present in both nuclear bag & nuclear chain fibres.
 - ✓ Secondary (**flower spray**) ending: only in nuclear chain fibres.

Nerve supply of spindles:

- **Intra fusar fibres:** Motor supply- γ (**gamma**) neurons exclusively supply intra fusar fibres.
- **Extra fusar fibres:** Motor supply- α (**alpha**) neurons . β fibres supply both intra fusar & extrafusar fibres.

MONOSYNAPTIC REFLEX: [STRETCH REFLEX]

- Contraction of the skeletal muscle when it is stretched along with its motor nerve.
- **Receptor:** muscle spindle.
- **Afferents:** Ia & II fibres.
- **Integration:** Spinal cord
- **Response:** Contraction of the skeletal muscle
- **Neurotransmitter:** Glutamic acid
- Most important characteristic is that it is highly developed in anti-gravity muscles.
- E.g.: Extensors of the legs & Flexors of the arms.
 - **Reaction time:** time b/w application of the stimulus & the response. 19-24 msec for knee jerk.
 - **Central delay:** time taken for the reflex activity to traverse the spinal cord. 0.6-0.9 msec.
 - E.g. Knee jerk, biceps jerk, triceps jerk (DTRs)

INHIBITION OF STRETCH REFLEXES:

- Reciprocal innervation or inhibition- Disynaptic inhibition.
- Inverse stretch reflex or autogenic inhibition. (receptor: Golgi tendon organ)

POLYSYNAPTIC REFLEXES: [WITHDRAWAL REFLEX]

- Eg: withdrawal reflex, abdominal & cremasteric reflexes
- **Withdrawal reflex:**
 - Contraction of flexor groups & inhibition of extensor groups. The stimulated limb is flexed and withdrawn from the stimulus. [Flexor response/flexor reflex]
 - With a stronger stimulus, extension of the opposite limb also occurs in addition. [Crossed extensor reflex]
 - Integration: Spinal cord **The superficial reflexes:**
- Plantar reflex: L5-S1
- Abdominal reflex: upper quadrants T 7-10, lower quadrant T10-12
- Cremasteric reflex: Center: L 1-2
- Anal reflex: Center: S 3-4
- Bulbo cavernous reflex
- Conjunctival & corneal reflex
- Light reflex & palatal reflex

Visceral reflexes:

- Micturition R.
- Defecation R.
- Erection R.
- The center of visceral reflexes is S 2, 3, 4.

DMA'S CORNER OF WISDOM

Deep reflexes:

- Knee jerk, ankle jerk, triceps jerk, biceps jerk, supinator jerk & jaw jerk.

SENSORY SYSTEM ASCENDING TRACTS IN THE SPINAL CORD

	Dorsal [post.] white column		Tracts in lateral white column		Tracts in ant. white column	
	Fasciculus gracilis [afferents from lower ½ of the body [Lumbar & Sacral]]	Fasciculus cuneatus [afferents from upper ½ of the body [Cervical & thoracic]	Lateral spino thalamic tract.	Dorsal spino cerebellar tract	Ventral spino cerebellar tract	Ventral spino thalamic tract
Origin	Axons of 1 st order neurons of Posterior root ganglion					
Course & Termination	• F.G Runs in the dorsal column of same segment upto midthoracic level. Above this level, it is pushed medially by F.C. • F.G→Nucleus gracilis • F.C→Nucleus cuneatus. • The middle part of the cuneatus nucleus, the pars rotundus is specific for Stereognosis.	•	• -fibres end in the Clarke's column of SC on the same side. • -The tract makes its appearance in segment C₇ to T₆. • - traverse via the inferior cerebellar peduncle from the medulla & ends in vermis of the cerebellum	• -fibres end in the Clarke's column of SC on the same side. • -The tract makes its appearance in segment L₃ to L₅ • -Extends upto the red nucleus, traverse via the superior cerebellar peduncle & ends in vermis of cerebellum	• -fibres end round the cells of the dorsal horn. Crosses to the opposite side and ends in the thalamus.	
Significance	✓ Conveys: ✓ -Fine touch ✓ -Tactile localization & discrimination ✓ - joint sense, position sense & Vibration sense	✓ Conveys: ✓ -all types of pain. ✓ -temperature ✓ [hot & cold]	✓ Conveys: ✓ Unconscious kinesthetic impulses essential for regulation of posture	✓ Conveys: ✓ Crude touch ✓ Tactile localization		

Course of lateral spinothalamic tract:

- Relays in dorsal horn cells of the S.C. -Histologically dorsal horn is divided into laminae I-VII, with I being the most superficial & VII the deepest. Lamina VII receives input from both the sides of the body, whereas other laminae receive only U/L inputs.
- Aδ- terminates in lamina I & V, C fibres in laminae IV & V.
- Axons of 2nd order neurons **cross** in anterior white commissure obliquely to opposite side & ascend to end in the thalamus.
- From the thalamus, 3rd order neurons start and traverse via the posterior limb of internal capsule & end in sensory cortex [post central gyrus].
- Unilateral section of this tract leads to complete loss of pain & temperature in the contralateral side. {Upto one segment below the level of lesion}.

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SENSORY CORTEX:

- **Primary somato sensory area (Brodmann No-3, 1, 2)** - post central gyrus. (Upside down representation of the body)
- Area 3- light touch, receive dense input from thalamus.
- Area 1, 2- deep stimuli such as pressure & joint movements, receive few thalamic fibres.
- Lesion in this area → C/L impairment of touch, pressure, Proprioception, two point discrimination & Stereognosis.
- **Secondary sensory area-parietal cortex.** Lesion results in altered pain perception.

PAIN

- **Sherrington definition-** physical adjunct of an imperative and protective reflex.
- Pain receptors- Nociceptors-naked nerve endings.
- **Aδ fibres-** small & myelinated, for fast pain, mediator - Glutamic acid, more sensitive to electric stimulus.
- **C fibres-** non myelinated, for slow pain, substance P is the NT, less sensitive to electric stimulus.
- **Theories for referred pain: convergence theory & facilitation theory.**

INHIBITION OF PAIN [ANALGESIA]

1. Stimulation produced analgesia:

a. **Segmental inhibition:** stimulation of the nerves of same segment by

1. Activation of group A afferent fibres.
2. Stimulation of the dorsal column which in turn activates the collaterals. **“GATE CONTROL THEORY”- Melzack and Wall.**

- **Gate:** The synaptic junctions between the peripheral nociceptor fibers and the dorsal horn cells of substantia gelatinosa in the spinal cord are the sites of plasticity. Hence, dorsal horn [substantia gelatinosa] is also called a gate, where pain impulses can be **gated** or modified.
- **Stimulation: Large fibres-** close the gate. **Small fibres-** open the gate.
- **Action of counter-irritants:** The pain relief produced by counter-irritants is primarily due to inhibition of pain pathways in the dorsal horn gate by stimulation of large diameter touch, pressure afferents.

b. **Supra spinal inhibition:**

- Mesencephalic pain inhibitory system –descending inhibitory pathway from brain stem to laminae I, IV & V. They contain opiate receptors.

2. Release of endogenous opioids:

OPIOID PEPTIDES

- OPIOID receptors seen in: **Brain & GIT**

The opioid peptides	Precursors
• Met – enkephalin, Leu – enkephalin, Octapeptide Heptapeptide	• Pro enkephalin
• β - endorphins & other endorphins	• Pro – Opio – melanocortin
• Dynorphin (1-8), Dyn (1-17), α - Neo endorphin, β - Neo endorphin	• Prodynorphin

Enkephalins:

- Found in the nerve endings of GIT & Brain.
- Act as synaptic transmitters.
- Also found in Substantia gelatinosa.
- decreases intestinal motility & have analgesic activity
 - ✓ **Proenkephalin:** - first identified in adrenal medulla.
 - ✓ **Pro – Opio – melanocortin** - Present in anterior & intermediate lobes of pituitary.
 - ✓ **Dynorphin (1-17)** - Found in duodenum
 - ✓ **Dynorphin (1-8)** :- Present in posterior pituitary
 - ✓ **Dynorphin (1-8) [(α & β) Neo endorphins]**: Present in hypothalamus

DMA'S CORNER OF WISDOM

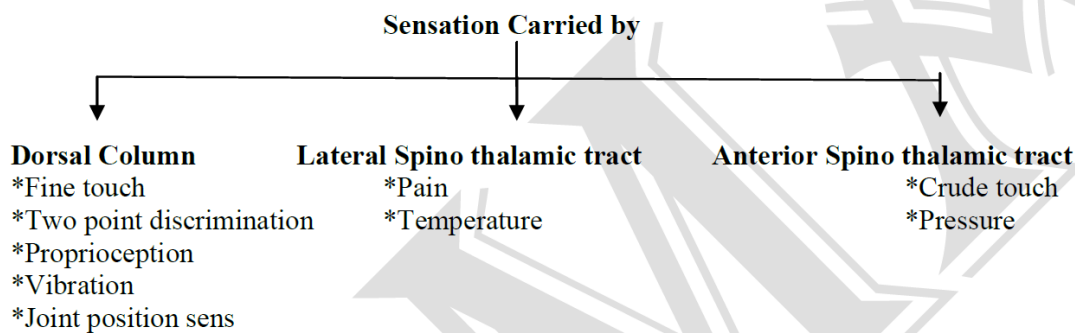
- Metabolism By enkephalinase (A&B) + Amino peptidase

OPIOID RECEPTORS

- Serpentine receptors, coupled to Gq, inhibit adenyl Cyclase

Receptor	Mechanism	Effects
μ (mu) ENDORPHINS BIND ONLY TO μ RECEPTORS	↑es K ⁺ Conductance	Analgesia, Constipation, Miosis, Euphoria, Sedation, Respiratory depression, ↑ed GH & Prolactin
K (Kappa)	Closure of Calcium Channels	Analgesia, Diuresis, Miosis, Sedation, Dysphoria
δ (delta)		Analgesia, Respiratory depression

- Pain sensitive structures of CNS:
 - ✓ Scalp
 - ✓ Aponeurotica
 - ✓ Middle meningeal artery
 - ✓ Dura mater/dural sinuses
 - ✓ Falx cerebri
 - ✓ Proximal portion of pial arteries



Cutaneous senses for which separate neural pathways exist	Synthetic senses (Combinations of sensations, patterns of stimulation, cortical components)
○ Touch, Warmth, Cold, Pain, Itching	○ Vibratory sense, 2 – Point discrimination, Stereognosis

MOTOR SYSTEM

MOTOR CORTEX:

- Primary motor area: **Area-4**- anterior to central sulcus (frontal lobes).
- origin of pyramidal tracts[Betz cells]
- Body is represented upside down.
- Size of representation α skill used for fine, voluntary movement.
- Supplementary motor area: involved in complex and planning voluntary movements.
- Premotor cortex: **Area-6**- anterior to pre central gyrus.
- Suppressor areas: anterior edge of precentral gyrus. [Area-4s]. 2s, 8s, 19s & 24s

DESCENDING TRACTS

- Pyramidal tracts.
- Extra pyramidal tracts.

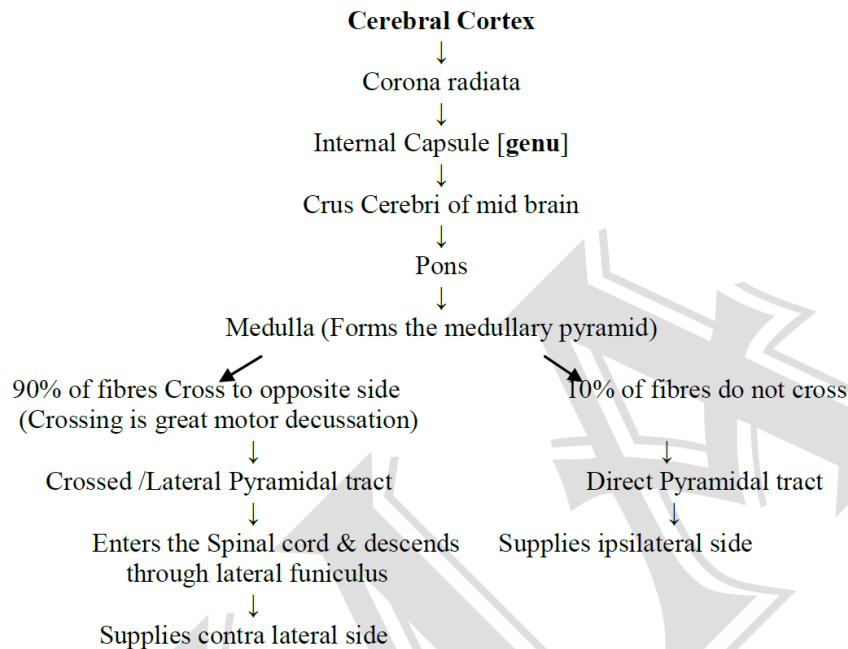
PYRAMIDAL TRACT

- Two Pyramidal Tracts, one on each side
- Arises from the Cerebral Cortex (Cortico spinal tract/ cortico bulbar tract)
- 60% - arises from Brodmann Area 4. Big pyramidal cells, the “**Betz cells**” are seen.

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- Rest - Supplementary motor area, Premotor area, Post central gyrus and posterior parietal cortex.
- **Course:** Below the brain stem, the fibres intermingle with extra pyramidal fibres to some extent.



Termination:

- Most PT fibres terminate in anterior or ventral horn cells.

Functions:

- Lateral C.S. Tract: Voluntary muscular contraction of distal limb muscles, fine discrete movements of fingers and hands.
- Anterior C.S. Tract: control the proximal muscle groups to carry out postural adjustments.
- Pathways for superficial reflexes.

Extra pyramidal tracts

Tracts	Origin	Major functions
Rubro spinal	• Red nucleus [M.B]	• Facilitation of flexor muscle tone
Tecto spinal & tecto bulbar	• Superior colliculus	• Postural movements in response to Visual & auditory stimuli
Reticulospinal	• Reticular formation [Pons & medulla]	• Regulate voluntary movement [mainly γ neurons], muscle tone, respiration, BP
Vestibulospinal	• Lateral vestibular nucleus	• Facilitation of anti gravity muscles
Medial longitudinal fasciculus	• Medial vestibular nucleus	• Coordination of reflex ocular movements & integration of eye & neck movements.

Lesion of pyramidal tracts:

- Commonest site: Internal capsule.
- Universal feature: Spasticity.

UPPER AND LOWER MOTOR NEURON DISEASES

UMN paralysis	LMN paralysis
• Muscles affected in groups and not individually	• Individual muscles may be affected
• Power decreased	• Very much decreased
• Atrophy slight	• Marked atrophy up to 70%
• Clasp knife Spasticity(hypertonia)	• Flaccidity(hypotonia)
• Superficial reflexes lost	• Lost

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• Exaggerated tendon reflexes	• Hypotonia and loss of tendon reflexes
• Clonus may be present	• Absent
• Babinski sign +(extensor plantar reflex)	• Babinski sign –ve
• Fasciculations absent	• Present
• Nerve conduction study normal	• Abnormal; denervation potential in EMG

Motor neuron disease:

- Acute: polio, Herpes Zoster, Coxsackie virus.
- Chronic:
 - ✓ Both UMN+LMN: Amyotrophic lateral sclerosis.
 - ✓ UMN type: Primary lateral sclerosis
 - ✓ LMN type: Progressive muscular atrophy.

Transection of the spinal cord

1. Complete transection:

- Causes: gunshot injury, dislocation of spine, occlusion of blood vessel.
- Commonest site of involvement- mid thoracic level.
 - **Stages:**
- I. **Stage of spinal shock/flaccidity:**
 - ✓ Muscle Tone- completely lost- hypotonia
 - ✓ Reflexes – lost/ decreased
 - ✓ Below the level of transection, all sensations are lost.
 - ✓ Paralysis of bladder & rectum, rapid recovery of sphincter vesicae- leading to urinary retention.
 - ✓ Occasional fall in BP, depending on the site of lesion.
- II. **Stage of reflex activity: [2 weeks after the injury]**
 - Smooth muscles- earlier to regain functions.
 - Hypotonia
 - Paraplegia in flexion.
 - No wasting of muscles.
 - Reflexes :
 - Babinski – positive
 - Appearance of Mass reflex.
 - Other reflexes- gradually become normal.

2. Incomplete transection: Same as 1 but with paraplegia in extension.

3. Hemi section of the spinal cord: BROWN SEQUARD SYNDROME.

Below the level of lesion	At the level of lesion	Above the level of lesion
• Ipsilateral loss: Fine touch, Proprioception, vibration & joint position • Contra lateral loss: Pain, temperature, crude touch & pressure	○ Same side: A. Sensory changes: complete anaesthesia B. Motor changes: complete LMN type of paralysis, complete & permanent vasomotor paralysis	○ Hyperesthesia- both sides.

4. Regional peculiarities :

- A. Hemisection at cervical region: constriction of pupil of the same side, loss of reflexes of upper limb, diaphragmatic palsy.
- B. Hemisection at lumbar region: micturition disturbances, loss of knee jerk.
- C. Hemisection at lumbosacral region: loss of bowel & bladder control.

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CEREBELLUM

Morphological & Functional divisions

Archicerebellum	Paleocerebellum	Neocerebellum
• Phylogenetically, Oldest part	• Next to develop	• Newest part to develop
• Made up of Flocculonodular lobe & the lingual	• Made up of anterior lobe (without lingula) and the pyramid and uvula	• Made up of the middle lobe (largest part of cerebellum) without pyramid and uvula
• Chiefly vestibular in Connections	• Connections are chiefly Spinocerebellar	•
• Controls the axial musculature and bilateral movements (used for locomotion and equilibrium)	• Controls tone, posture and crude movements of the limbs	• Concerned with the regulation of fine movements
• Output passes directly to brain stem	• Output to brainstem passes through Emboliform, fastigial or globose nuclei	• Output goes to Venterolateral nucleus of thalamus through dentate nucleus

- **Layers (3):**
 - ✓ External molecular layer,
 - ✓ Purkinje cell layer and
 - ✓ internal granular layer.
- **Deep nuclei (4):**
 - ✓ Dentate,
 - ✓ Emboliform
 - ✓ Fastigial and
 - ✓ globose.
- **Purkinje Cells:**
 - Biggest neurons in the body.
 - Their axons are the only output from Cerebellar cortex.
 - Dendritic trees of purkinje cells are flattened.
 - Output from the purkinje cells are always inhibitory.
- **Granule Cells**
 - Receive input from mossy fibres and innervate the purkinje cells.
 - Their cell bodies are present in granular layer.
 - Each sends an axon to molecular layer and forms parallel fibres.
- **The output of granule cells is always excitatory whereas the output from other cells is always inhibitory.**
 - **Neurotransmitters Released:**
 - ✓ **Granule cells** – Glutamate:
 - ✓ **Others-** GABA
 - Basal electric rhythm of cerebellum: 150-300/sec.
- **Neurons in Cerebellar Cortex (5):**
 - ✓ Purkinje,
 - ✓ granule,
 - ✓ basket,
 - ✓ stellate and
 - ✓ golgi cells.
- Two main afferents to Cerebellar Cortex are **mossy fibers and Climbing fibers.**
- **Basket Cells**
 - Located in molecular layer.
 - Receive inputs from parallel fibres and projects to purkinje cells.
- **Stellate Cells** – more superficial but similar to basket cells.
- **Golgi cells**
 - Located in granular layer.
 - Dendrites project into molecular layer & receive inputs from parallel fibres
 - Their axons project into dendrites of the granule cells

FUNCTIONS:

- **Flocculo nodular lobe- body posture & equilibrium.** [removal of the lobe-abolishes motion sickness]
- **Anterior lobe:** medial part- inhibits **muscle tone**.
Lateral part- facilitates muscle tone.
- **Coordination of movements**

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THALAMUS

	Nucleus	Afferent	Efferent	Functions
Non specific projection nuclei	Anterior group	Mamillary body (Hypo thalamus) Mamillo thalamic tract	Cingulate cortex [Area 24]	-Forms part of papez circuit - limbic system- recent memory & emotions
	Midline	From spino thalamic, trigemino thalamic, medial lemniscus, reticular formation, other thalamic nuclei, hypothalamus	To hypothalamus, neocortex, basal ganglia, other thalamic nuclei	Centre for integrating crude visceral and somatic sensations
	Intra laminar	From RAS, basal ganglia & other thalamic nuclei.	To prefrontal cortex	Integrates sensory impulses, responsible for alerting effects of RAS
	Dorso medial	From hypothalamus & pre frontal cortex	To pre frontal cortex (Area- 8, 9, 10, 11)	Association centre for synthesis of crude somatic sensations
specific projection nuclei	Lateral ventral	From dentate nucleus of cerebellum, from globus pallidus via thalamic fasciculus	To cerebral cortex (pre motor areas 4 & 6) via post. limb of internal capsule	Relay voluntary motor functions
	Postero ventral	Termination of spinothalamic tracts, medial lemniscus, termination of trigeminal lemniscus	To sensory cortex 3, 1, 2 via post. limb of internal capsule	Relay somatosensory impulses [touch, pain, pressure, temperature] from the trunk & sensory impulses from the face.
	Dorsal lateral	From other thalamic nuclei; Parietal lobe of cerebral cortex	To cerebral cortex	Language & speech
	Pulvinar	From other thalamic nuclei; cerebral cortex	To cerebral cortex	Auditory, visual & somatic information
	MGB	From cochlear nuclei & inferior colliculi	To auditory cortex via internal capsule	Hearing
	LGB	From optic tract	To I/L calcarine cortex	Vision

MAJOR LEVELS OF MOTOR INTEGRATION

Level of integration	Principal function
Spinal cord	Control of spinal reflexes- stretch reflex,
Medulla	Anti gravity reflexes, regulation of heart & respiration rate. Tonic labyrinthine & tonic neck reflexes.
Midbrain	Righting reflexes
Midbrain, thalamus	Locomotor reflexes
Hypothalamus, limbic system	Emotional functions
Cerebral cortex	Initiation of voluntary movements, emotions and memory; involved in conditioned reflexes. Optical righting reflexes, placing & hopping reactions

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EEG

- Also called Berger Rhythm

	Beta (β) wave	Alpha (α) wave	Theta wave	Delta wave
Area of origin	Parietal & Frontal region	Parieto – Occipital area	Hippo Campus	
Seen in	Drowsiness, Children, Patients awake with eyes open	Awake Patient at rest with eyes Closed	Children & drowsiness	Deep NREM sleep & Infants
Frequency	High (>14HZ)	8-13 HZ	Low (4.7 HZ)	Very Low (3-HZ)
Amplitude	Low	High	Very High	Maximum

EEG PATTERNS IN SLEEP

Non-Rapid Eye Movement (NREM) 70-80% of sleep Slow wave / orthodox sleep				Rapid Eye movement (REM)/Paradoxical sleep (20-30% of sleep)
STAGE – I (dozing)	STAGE – II (unequivocal)	STAGE – III	STAGE – IV	Light phase of sleep, arousal is difficult. Dreaming is seen in active sleep
First & lightest stage Theta waves	Sleep Spindles, K – Complex easily evoked	Delta waves first appear	Predominant Delta activity	
Sleep disorders of NREM: - Somnambulism - Somniloquy (sleep talks) - Pavor nocturnus (night terror) - Nocturnal enuresis - Bruxism				Sleep disorders of REM: - Night mares - Narcolepsy - Nocturnal penile tumescence

SLEEP CYCLE:

- 90 minutes of NREM → 20 minutes of REM → NREM Sleep.
 - REM occurs about 4-6 times through the night.
 - More of REM sleep in the later part of night towards morning hours.
 - A subject wakes up in the morning from REM sleep.
 - Stages III & IV are more in children.
- Note:**
 - Dreams can occur in both REM and NREM sleep. NREM dreams are not registered in memory.
 - REM dreams are associated with more bodily muscle activity.
- In a normal EEG.,**
 - ✓ Alpha wave → most striking component & reflects the Synchronized brain activity
 - ✓ Alpha block → by eye opening, alpha rhythm is replaced by beta wave.
 - ✓ Desynchronisation → Replacement of alpha waves by other waves (Alerting/Arousal response)

Sleep zones in the brain:

- ✓ Diencephalic sleep zone.
- ✓ Medullary synchronizing zone.
- ✓ Basal fore brain sleep zone.

BASAL GANGLIA

- Group of nuclei in the fore brain & upper part of brain stem that have motor functions of great importance. It includes:
 - Caudate nucleus
 - Putamen
 - Globus pallidus- Paleo striatum
- Caudate. N & putamen - forms the corpus striatum/ Neo striatum
- Globus Pallidus & Putamen together forms- lenticular nucleus

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